Co-pending Application No. 10/119,118 has been abandoned in favor of a continuation filed on October 20, 2004, Application No. 10/969,140 (Atty. Docket No. 3406/3/US), thereby obviating this preliminary rejection.

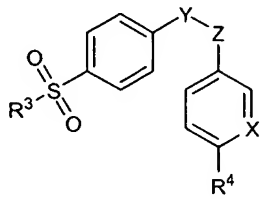
35 U.S.C. §103(a) rejections

1. Tanida

Reconsideration is respectfully requested of the rejection of claims 1-5, 8-12, 14-16, 24-29, 31-40, 43-47, 49, 50, 58-63, 65-70, 72-78, and 82-86 under §103(a) as unpatentable over Tanida (WO 98/05310; all citations are to the English equivalent, U.S. 6,214,378).

Claims 1-5, 8-12, 14-16, 24-29, 31-35

Claim 1 is directed to an orally deliverable pharmaceutical composition comprising (a) a selective cyclooxygenase-2 inhibitory drug of low water solubility having the formula



where X, Y, Z, R^3, and R^4 are as defined in the claim; (b) a pharmaceutically acceptable solvent liquid selected from the group consisting of glycols and glycol ethers; and (c) a turbidity-decreasing polymer. The claim also requires that at least a substantial portion of the drug is in dissolved or solubilized form in the solvent liquid, and that said polymer is present in an amount sufficient to substantially inhibit crystallization and/or precipitation of the drug in simulated gastric fluid. Such crystallization inhibition is desirable, as stated in the instant specification, because "there is often a tendency, particularly for a crystalline drug of low water solubility, to precipitate out of solution and/or crystallize when the drug comes in contact with water, for example in the aqueous environment of the gastrointestinal tract. Such precipitation and/or re-crystallization can offset or reduce the potential rapid onset benefits sought by formulating the drug as a solution." See page 1, lines 17-24.

Tanida describes capsules for oral preparations of active agents. According to the Background of the Invention section, "[Tanida's] invention relates to capsules being able to be administered orally in which pharmacologically active substance depending upon the object can be encapsulated and which is firstly disintegrated upon arriving at the large intestine whereby the pharmacologically active substance can be efficiently released therefrom ... ." (See col. 1, lines 9-15; emphasis added). Regarding the active agent that may be thus encapsulated, Tanida acknowledges that "[t]here is no particular limitation ... so far as it is a substance which is effective when released in the lower gastrointestinal tracts and any of such substances may be used." (See col. 3, lines 11-15). As Applicants have previously mentioned, Tanida describes twelve categories of pharmacologically active substances suitable for use with the capsules Tanida discloses; one category is anti-inflammatory agents (see col. 3, lines 17-22). Eighty-six specific

examples of active agents are listed (see col. 3, lines 22-52), including celecoxib (see col. 3, line 41). Tanida states that a preferred anti-inflammatory agent is a COX-2 inhibitor (see col. 3, lines 56-57). In Examples 3-11, Tanida describes the preparation of capsules containing prednisolone, calcitonin, 5-fluorouracil, sodium betamethasone phosphate, budesonide, and diclofenac sodium.

The Office asserts that the claimed compositions would have been obvious to one skilled in the art having knowledge of the teachings of Tanida. However, the Office appears to neglect the requirement in claim 1 that the turbidity-decreasing polymer is present in an amount sufficient to substantially inhibit crystallization and/or precipitation of the drug in simulated gastric fluid. As stated in the subject specification, "a drug administered in imbibable solution can be available for absorption higher in the alimentary tract, for example, in the mouth and esophagus, than one that becomes available for absorption only upon disintegration of the carrier formulation in the stomach or bowel." See page 9, line 31 through page 10, line 2.

The Office has not shown why one skilled in the art, provided with Tanida's teaching of a capsule designed to firstly disintegrate upon arriving at the large intestine, would have been motivated to prepare the claimed compositions that are clearly intended for distribution of a COX-2 inhibitor at a point earlier in the GI tract. The Office has not because it cannot. Tanida teaches away from the claimed compositions, and modification of Tanida's teachings to yield a composition suitable for absorption of an active agent prior to its arrival at the lower intestine would render Tanida's capsules unsatisfactory for their intended purpose. Thus, there is no suggestion or motivation to make the modification proposed by the Office, and therefore claim 1 is patentable over Tanida. See MPEP 2143.01.

Claims 2-5, 8-12, 14-16, 24-29, 31-35 depend from claim 1, and are patentable over Tanida for the reasons stated above with respect to claim 1, and for the additional features that they add.

Claim 36-40, 43-47, 49, 50, 58-63, and 65-69

Claim 36 is directed to an orally deliverable pharmaceutical composition comprising (a) a selective cyclooxygenase-2 inhibitory drug of low water solubility having the formula shown above for claim 1; (b) a pharmaceutically acceptable solvent liquid selected from the group consisting of glycols and glycol ethers; and (c) a cellulosic polymer. The claim also requires that at least a substantial portion of the drug is in dissolved or solubilized form in the solvent liquid, and that said cellulosic polymer is present in an amount sufficient to substantially inhibit crystallization and/or precipitation of the drug in simulated gastric fluid.

Claim 36 is patentable over Tanida for the reasons set forth above with respect to claim 1. The Office has not shown why one skilled in the art, provided with Tanida's teaching of a capsule designed to firstly disintegrate upon arriving at the large intestine, would have been motivated to prepare the claimed compositions that are clearly intended for distribution of a COX-2 inhibitor at a point earlier in the GI tract. Indeed, there is no suggestion or motivation to modify Tanida to arrive at the compositions of claim 36, and therefore claim 36 is patentable over Tanida. Claims 37-40, 43-47, 49, 50, 58-63, and 65-69 depend from claim 36 and are patentable over Tanida for the reasons stated above with respect to claim 36, and for the additional features that they add.

Claims 70, 72-78, 82, and 83

Claim 70 is directed to an orally deliverable pharmaceutical composition comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility (having the formula show above for claim 1) in a high energy phase together with one or more pharmaceutically acceptable excipients, encapsulated within a capsule wall that comprises a turbidity-decreasing polymer in an amount effective to substantially inhibit crystallization and/or precipitation of the drug in simulated gastric fluid. For the same reasons given above with respect to claims 1 and 36, claim 70 is patentable over Tanida. Claims 72-78, 82, and 83 depend from claim 70, and are patentable over Tanida for the reasons stated above with respect to claim 70, and for the additional features that they add.

Claims 84-86

Claims 84-86 depend from claims 1, 36, or 70, and are patentable over Tanida for the reasons stated above with respect to claims 1, 36, and 70, and for the additional features that they add.

2. Tanida in view of Hanna

Reconsideration is respectfully requested of the rejection of claims 17-19, 51-53, and 79-81 under §103(a) as unpatentable over Tanida in view of Hanna (U.S. 4,601,894).

Claims 17-19 depend from claim 1, and are directed to compositions according to claim 1 wherein the turbidity-decreasing polymer is hydroxypropylmethylcellulose having methoxyl and hydroxypropoxyl substitution within the claimed ranges. Claims 51-53 depend from claim 36 and claims 79-81 depend from claim 70. Like claims 17-19, claims 51-53 and 79-81 are directed to compositions according to claims 36 and 70, respectively, wherein the cellulosic polymer is hydroxypropylmethylcellulose having methoxyl and hydroxypropoxyl substitution within the claimed ranges.

Hanna describes oral controlled release matrix dosage forms combining acetaminophen, pseudoephedrine (or a salt thereof), and dexbrompheniramine; a polymer; and excipients. HPMC ethers and ethylcellulose are "particularly contemplated" as the required polymer. Certain commercially-available HPMC ethers are listed; several have methoxyl and hydroxyl substitution within the ranges of claims 17-19, 51-53, and 79-81. For example, according to the website http://www.dow.com/methocel/resource/chem.htm (a copy of which is enclosed), METHOCEL K has 22% methoxyl substitution and 8.1% hydroxypropyl substitution.

The fact that Hanna with Tanida *may be* combined does not change the fact that one skilled in the art would not have been motivated to combine these references to arrive at the claimed compositions. As noted above, Tanida's invention relates to capsules for oral administration which does not disintegrate until arrival in the large intestine, while the claimed compositions are contemplated for use in situations when absorption higher in the alimentary tract is desired. Hanna does not add what Tanida is missing, and claims 17-19, 51-53, and 79-81 are patentable over Tanida in view of Hanna.

3. Tanida in view of Guess

Reconsideration is respectfully requested of the rejection of claims 13 and 48 under §103(a) as unpatentable over Tanida in view of Guess (U.S. 6,054,455).

Claim 13 depends from claim 1 and claim 48 depends from claim 36. Both claims 13 and 48 require that the COX-2 inhibitor is valdecoxib.

Guess describes tachykinin receptor antagonists, e.g., a neurokinin-1 receptor antagonist, useful for treatment or prevention of nonbacterial prostatitis and/or prostatodynia. Guess mentions that the tachykinin receptor antagonist may be administered in combination with another drug, including a selective COX-2 inhibitor (see col. 32, lines 48-54). Several selective COX-2 inhibitors are named, including celecoxib and valdecoxib (see col. 33, lines 18-19). Compositions in the form of tablets, pills, capsules or wafers for oral administration are particularly preferred (see col. 32, lines 27-28).

The combination of Tanida's compositions that deliver an active agent to the large intestine with Guess's tachykinin receptor antagonists would not have directed one skilled in the art to the compositions defined by claims 13 or 48, both of which contemplate situations where absorption of valdecoxib higher in the alimentary tract is desired. Claims 13 and 48 are patentable over Tanida in view of Guess.

4. Tanida and Black

Reconsideration is respectfully requested of the rejection of claims 20-23, 54-57, and 84-91 under §103(a) as unpatentable over the combined disclosure of Tanida and Black (U.S. 5,733,909).

Claim 20 depends from claim 1, and is directed to the composition of claim 1 further comprising a vasomodulator, wherein the selective cyclooxygenase-2 inhibitory drug and the vasomodulator are present in total and relative amounts effective to relieve pain in headache or migraine. Claim 21 is directed to the composition of claim 1 further comprising an alkylxanthine compound, wherein the selective cyclooxygenase-2 inhibitory drug and the alkylxanthine compound are present in total and relative amounts effective to relieve pain in headache or migraine. Claims 22 and 23 depend from claim 21 and specify the nature of the alkylxanthine compound.

Claim 54 depends from claim 36, and is directed to the composition of claim 36 further comprising a vasomodulator, wherein the selective cyclooxygenase-2 inhibitory drug and the vasomodulator are present in total and relative amounts effective to relieve pain in headache or migraine. Claim 55 is directed to the composition of claim 36 further comprising an alkylxanthine compound, wherein the selective cyclooxygenase-2 inhibitory drug and the alkylxanthine compound are present in total and relative amounts effective to relieve pain in headache or migraine. Claims 56 and 57 depend from claim 55 and specify the nature of the alkylxanthine compound.

Claims 84-91 depend from claims 1, 36, or 70, and are directed to methods of treating certain conditions or disorders comprising administering an oral composition according to claim 1, 36, or 70.

Claims 20-23, 54-57, and 84-91 are patentable over Tanida in view of Black. Black describes *prodrugs* of COX-2 inhibitors (not active COX-2 inhibitors of the formula required by claims 1, 36, and 70) that may also be administered as a salt. Examples of suitable salts are described at col. 8, lines 1-55. One

example from the dozens given is the caffeine salt; no significance is placed on the selection of caffeine from the dozens of organic bases described. Furthermore, Black does not describe administering the prodrug compound in combination with caffeine, but rather administering the prodrug as a salt formed by reaction of the prodrug with caffeine or other cyclic amine. Furthermore, nothing in Black changes Tanida's teaching of compositions that deliver an active agent to the large intestine, unlike the compositions of claims 20-23, 54-57, and 84-91.

5. Tanida in view of Kawata

Reconsideration is respectfully requested of the rejection of claim 74 under §103(a) as unpatentable over Tanida in view of Kawata (U.S. 4,343,789).

Claim 74 depends from claim 70, and requires that the COX-2 inhibitor is in an amorphous phase.

Kawata describes compositions that contain an amorphous solid medical material. The combination of Tanida and Kawata would not have led one skilled in the art to the composition of claim 74. Claim 74, like claim 70, requires that the turbidity-decreasing polymer is present in an amount effective to substantially inhibit crystallization and/or precipitation of the drug in simulated gastric fluid. Tanida, alone or taken together with Kawata, teaches compositions that deliver an active agent to the large intestine. Claim 74 is patentable over Tanida in view of Kawata.

Conclusion

The Applicants submit that the present application is now in condition for allowance. Early allowance of all pending claims is respectfully solicited.

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Enclosures:

Transmittal Letter
Amendment Transmittal
Response to Office Action
Enclosure (3 pgs)
Itemized Postcard